ENANTIOCONTROLLED SYNTHESES OF THE CUPARENE SESQUITERPENES, (-)-HERBERTENE, (+)-β-CUPARENONE, (-)-DEBROMOAPLYSIN, AND (-)-APLYSIN

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Summary: Enanticontrolled syntheses of the Cuparene sesquiterpenes, (-)-herbertene, (+)- β -cuparenone, (-)-debromoaplysin, and (-)-aplysin, have been achieved starting from the optically active tricyclic dienone by employing a Fischer indolization reaction under non-acidic conditions as the key step.

Owing to its biased structure, the optically active tricyclic dienone 1, accessible readily from dicyclopentadiene,^{1,2} undergoes electrophilic reaction at β carbon and nucleophilic reaction at α center (after saturation of the enone double bond) with virtually complete *exo*-face selectivity. However, difficulty in direct introduction of an aryl group as well as the functional groups having sp² and sp orbitals at α carbon center restricts its extensive use as a versatile chiral building block.³ We now describe a method for the stereoselective introduction of an aryl group at α center employing a Fischer indolization reaction under non-acidic conditions⁴ which could be utilized for the syntheses of the cuparenone sesquiterpenes, (-)-herbertene⁵ (2), (+)- β cuparenone^{6,7} (3), (-)-debromoaplysin^{8,9} (4), and (-)-aplysin^{9,10} (5) (Scheme 1).



When the α -methylketone 6, obtained in 73% yield from the optically pure dienone¹¹ 1 in two steps,^{3f} was refluxed with *p*- or *o*-tolylhydrazine hydrochloride in aqueous pyridine (1:10) at reflux temperature, facile reaction occurred to give the corresponding pentacyclic carbinol amines 10, as a single product¹² 10a, $[\alpha]_D^{31+122.4^\circ}$ (*c* 1.11), from the former and as a mixture of two regioisomers 10b and 10c from the latter in 72 and 75% yields, respectively. In each reaction the aryl group was introduced diastereospecifically from the convex face without damaging the acid-sensitive double bond under these non-acidic conditions.



Reagents: (a) (i) Zn, AcOH, EtOH, reflux, (ii) LDA, MeI, THF, 73%; (b) NaNO₂, H₃PO₂, 0 °C.

The amine¹² 10a, on diazotization reaction under the reductive conditions,¹³ afforded the ketone¹² 11a, $[\alpha]_D^{29} + 210.6^{\circ}$ (c 1.10), in 70% yield as a single product. Very interestingly, the latter mixture 10b/c, on the same treatment, furnished the ketone 11b, mp 77-78 °C, $[\alpha]_D^{30} - 250.9^{\circ}$ (c 1.03), and the hemi-ketal 12 in yields of 28 and 21%, respectively, as a single product (Scheme 2). Specific formation of the hemi-ketal 12 in the latter mixture was presumed to be due to the steric hindrance in the 1,2,3-trisubstituted aryl isomer 10c in which reduction was suppressed by neighboring methyl group to give rise to the observed product by intervention of the ketoxonium intermediate 14 (Scheme 3).



Upon thermolysis in refluxing o-dichlorobenzene, both of the isomeric ketones $11a^{12}$ and 11b afforded the corresponding cyclopentenones 15a, $1^2 [\alpha]_D^{31} + 2.9^\circ$ (c 1.03), and 15b, $[\alpha]_D^{24} + 7.68^\circ$ (c 0.96) [lit. 7b; $[\alpha]_D^{24} + 7.1^\circ$ (c 1.16, CHCl₃)], in 71 and 78% yields, respectively, by retro-Diels-Alder reaction. Reaction of these with methyllithium followed by oxidation furnished the corresponding enones 17a, $1^{2,14}$

 $[\alpha]_D^{27} -209.8^{\circ}$ (c 1.17), and 17b, ¹⁴ $[\alpha]_D^{29} +233.3^{\circ}$ (c 1.32) [lit.: $[\alpha]_D^{20} +253^{\circ}$ (c 1.7, CHCl₃)^{7a}; $[\alpha]_D^{24} +236^{\circ}$ (c 1.02, CHCl₃)^{7b}], in 53 and 87% yields, which were then treated with dimethylzinc^{7a} to give the cyclopentanones, 18a, ¹² $[\alpha]_D^{32} -41.0^{\circ}$ (c 1.28), and 18b, $[\alpha]_D^{27} +44.6^{\circ}$ (c 0.57), in yields of 53 and 74%, respectively. The latter was identical with (+)- β -cuparenone (3), $[\alpha]_D^{30} +45.0^{\circ}$ (c 1.4, CHCl₃).^{7a} The former ketone¹² 18a was further transformed into the dithiane¹² 19a, $[\alpha]_D^{29} -30.0^{\circ}$ (c 1.23), in 85% yield which on desulfurization with Raney nickel afforded (-)-herbertene (2), $[\alpha]_D^{27} -48.9^{\circ}$ (c 0.32) [natural⁵: $[\alpha]_D -48.3^{\circ}$ (c 1.31, CHCl₃)] in 47% yield. This constitutes the first enantio-controlled synthesis of this terpenoid (Scheme 4).



Scheme 4

Reagents: (a) o-DCB, reflux, (b) MeLi, THF, (c) Jones oxidation, (d) Me₂Zn, Ni(acac)₂, Et₂O, (e) CH₂(CH₂SH)₂, BF₃'OEt₂, (f) Raney Ni, EtOH, room temperature.

On the other hand, upon diazotization reaction in aqueous methanol,¹⁵ the mixture 10b/c furnished the keto-ether 20 and the acetal 21 in 34 and 33% yield. The ketone 20 was then alkylated with methyl iodide in the presence of lithium diisopropylamide to give 22, mp 105-106 °C, $[\alpha]_D^{31}$ -158.4° (c 1.0), which on thermolysis as above afforded the cyclopentenone 23, $[\alpha]_D^{30}$ -61.1° (c 1.07), in 51%



Scheme 5

Reagents: (a) NaNO₂, conc. H₂SO₄ (cat.), MeOH, (b) LDA, MeI, THF, (c) o-DCB, reflux, (d) MeLi, THF, (e) PCC, CH₂Cl₂, (f) BBr₃, (CH₂Cl₂, 80 °C, (g) ⁱBu₂AlH, CH₂Cl, then 10% aq. HCl, (h) H₂, PtO₂, EtOH, (i) NBS, CCl₄, reflux.

Reaction of 23 with methyllithium followed by oxidation of the overall vield. resulting allylic alcohol mixture 24 gave the single enone 25, $[\alpha]_D^{31} + 245.4^\circ$ (c 1.08), in 67% overall yield, whose ether bond was cleft with boron tribromide¹⁶ to give the phenol 26, mp 183-183.5 °C, $[\alpha]_D{}^{30}$ +246.8° (c 1.11), in 60% yield. Reduction of 26 with diisobutylaluminum hydride brought about spontaneous cyclization of the product 27 to furnish the tricyclic ether⁹ 28, $[\alpha]_D^{30}$ -124.9° (c 0.61), in 60% yield after Hydrogenation¹⁷ of **28** proceeded in a work-up with diluted hydrochloric acid. stereospecific way from the convex face to give (-)-debromoaplysin (4), $[\alpha]_D^{29}$ -66.5° (c 0.72) [natural⁹: $[\alpha]_D^{21}$ -68°], in 83% yield. Upon exposure to N-bromosuccinimide, 4 afforded (-)-aplysin (5), mp 84.5-85.5 °C, $[\alpha]_D^{32}$ -83.5° (c 0.31) [natural¹⁰: mp 85-86 °C, $[\alpha]_D^{27}$ -85.4° (CHCl₃)], in 87% yield. Since the former chiral synthesis⁹ has been achieved by optical resolution in the later stage, the present instance constitutes virtually the first enantiocontrolled synthesis of these two natural terpenoids (Scheme 5).

References and Notes*

- All new compounds gave the expected analytical (combustion and/or high resolution mass) and spectral (IR, NMR, and mass) data. All optical rotations were measured in chloroform solution.
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